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## Molecular radiotheragnostics in thyroid disease

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### ABSTRACT

Molecular radiotheragnostics directly links nuclear medicine diagnostic imaging to therapy. The imaging study is used to detect a specific molecular target associated with a disease process. A radiotherapeutic molecule with a similar biodistribution to the diagnostic agent can then be used to deliver targeted therapy.

Molecular radiotheragnostics have been applied to manage both benign and malignant thyroid disease since the 1940s. The specific molecular pathway targeted is the sodium/iodide symporter (NIS) located on the basolateral membrane of the thyroid follicular cell. Radiolabelling of iodide or a similar ion

allows targeting of the NIS system with radiopharmaceuticals for imaging ( $^{123}\text{I}$ -radioiodine and  $^{99\text{m}}\text{Tc}$ -pertechnetate) and treatment ( $^{131}\text{I}$ -radioiodine) by virtue of their gamma ray and beta-particle emissions, respectively.

Scintigraphic imaging directly guides  $^{131}\text{I}$ -radioiodine treatment planning to maximise therapeutic benefit while minimising adverse reactions, in a personalised medicine approach.

### Principles

Molecular radiotheragnostics combine nuclear medicine diagnostic imaging with treatment. Imaging is used to detect a specific molecular target associated with an underlying disease process. A radiotherapeutic molecule with a similar biodistribution to the imaging radiopharmaceutical can then be used to deliver targeted therapy.<sup>1</sup>

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Molecular radiotheragnostics have been applied to thyroid disease since the 1940s when radioiodine was first used to treat thyroid disorders.<sup>1</sup> Subsequent gamma camera development in the 1950s then made imaging possible.<sup>2</sup> The specific molecular pathway targeted is the sodium/iodide symporter (NIS). NIS-mediated iodide accumulation within the thyroid is central to molecular thyroid theragnostics. Radiolabelling of iodide or similar ions allows targeting of the NIS-system for imaging and therapy.<sup>1</sup>

### The sodium/iodide symporter

Iodine is essential for the synthesis of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Iodide ions are taken up by the NIS, a basolateral transmembrane protein on the thyroid follicular cells that actively co-transport sodium and iodide ions into cells against a concentration gradient.<sup>3</sup> Iodide is then translocated across the apical cell membrane and oxidised by thyroid peroxidase. Iodination of the tyrosine residues of thyroglobulin (colloid protein) then takes place (organification). Thyroglobulin is the precursor of thyroid hormone synthesis.

NIS expression is upregulated by thyroid-stimulating hormone (TSH) and downregulated by thyroglobulin and anti-thyroid medications. NIS is also expressed by non-thyroidal tissues, eg salivary and lacrimal glands, stomach, lactating breast, placenta, kidneys and thymus.<sup>4,5</sup>

### Thyroid theragnostic radiopharmaceuticals

Theragnostic radiopharmaceuticals emit ionising radiation as gamma rays and/or beta-particles, allowing scintigraphic imaging and therapy, respectively (Table 1). The NIS-system can be targeted specifically using radioactive iodide (I) or pertechnetate ions, which share similar chemical properties.

#### Key points

Molecular radiotheragnostics use nuclear medicine diagnostic imaging to detect a specific molecular target. A radiotherapeutic molecule with a similar bio-distribution can then be used to deliver targeted therapy

In thyroid disease, the specific molecular pathway targeted is the sodium/iodide symporter (NIS)

NIS-mediated iodide (or a similar ion) accumulation within the thyroid is central to molecular theragnostics in both benign and malignant thyroid disease

<sup>99m</sup>Tc-pertechnetate and <sup>123</sup>I-radioiodine are used for imaging and <sup>131</sup>I-radioiodine for treatment. <sup>99m</sup>Tc-pertechnetate is not the imaging agent of choice for thyroid cancer imaging

Imaging is useful to plan therapy and optimise a personalised medicine approach

**KEYWORDS:** <sup>99m</sup>Tc-pertechnetate, DTC (differentiated thyroid cancer), molecular, NIS (sodium/iodide symporter), radioiodine, radiotheragnostic, thyroid, thyrotoxicosis ■

Labelled with the gamma-emitter technetium-99m (<sup>99m</sup>Tc), pertechnetate ions are taken up via the NIS into thyroid follicular cells where they are trapped but not organified.<sup>6</sup> <sup>99m</sup>Tc-pertechnetate is the first-line scintigraphic diagnostic thyroid imaging agent for the investigation of benign thyroid disease, is readily available and is inexpensive. Reduced NIS expression by malignant thyroid cells leads to low pertechnetate uptake, giving a 'cold nodule' appearance.

<sup>123</sup>I-radioiodine decays by gamma ray emission and, unlike pertechnetate, is organified by the thyroid so can be used to characterise poorly functioning retrosternal thyroid tissue, for thyroid cancer imaging and for personalised treatment dose planning. Disadvantages include the relative cost, availability and 13-hour half-life.

<sup>131</sup>I-radioiodine has an 8-day half-life and decays by gamma ray and beta-particle emission allowing both imaging and targeted therapy. <sup>131</sup>I beta particles travel only short distances through tissue (average 0.4 mm) and cause cell death directly by radiation-induced DNA damage or indirectly through free-radical formation.

### Benign thyroid disease

Molecular radiotheragnostics in benign thyroid disease are applied in the imaging and treatment of

- hyperthyroidism due to solitary toxic nodule, toxic multinodular goitre or Graves' disease (relapsed or first-line treatment)
- large non-toxic goitre to reduce gland volume in non-surgical candidates.<sup>7</sup>

Scintigraphic imaging with <sup>99m</sup>Tc-pertechnetate or, less frequently, radioiodine provides visual assessment of activity distribution within the thyroid reflecting physiological and pathophysiological NIS-mediated iodide uptake. Imaging confirms the cause of hyperthyroidism and can be used to assess feasibility of <sup>131</sup>I as a therapeutic option and to guide activity prescription.

Anti-thyroid drugs, exogenous iodine, thyroxine and amiodarone all interfere with NIS-mediated thyroid radiopharmaceutical uptake and are withheld for varying periods before imaging (Table 2).<sup>8</sup> Uptake of activity reflects metabolic function and may be quantified as a percentage of the administered activity to guide treatment.

Amplified follicular cell NIS expression in Graves' disease results in globally increased iodide uptake, shown as diffuse, increased radiopharmaceutical activity throughout the gland on imaging. Toxic multinodular glands show increased NIS expression in 'hot' hyperfunctioning nodules and reduced levels in 'cold' nodules. Increased NIS levels in autonomously functioning nodules manifest as increased radiopharmaceutical uptake within the nodule (Fig 1).<sup>9</sup>

Following the same NIS-uptake pathway, <sup>131</sup>I can be used to deliver targeted beta-particle therapy. Treatment aims are to cure hyperthyroidism and achieve a euthyroid or hypothyroid state.<sup>7,10</sup> UK guidelines recommend fixed treatment activities between 400 and 800 MBq depending on gland size, underlying aetiology and patient comorbidities. In practice, most patients receive 400–600 MBq.<sup>11</sup>

Thyroid function is usually controlled with anti-thyroid drugs before treatment to reduce the risk of 'thyroid storm'

**Table 1. Properties of thyroid theragnostic radiopharmaceuticals**

Properties	Radiopharmaceutical		
	<sup>131</sup> I-radioiodine	<sup>123</sup> I-radioiodine	<sup>99m</sup> Tc-pertechnetate
Production	Reactor	Cyclotron	Generator
Half-life	8 days (long half-life allows transport some distance from production)	13 hours (longer half-life allows transport some distance from production)	6 hours (short half-life favours on site production)
Radioactive method of decay	Gamma ray and beta particles	Gamma ray	Gamma ray
Gamma ray energy peak (140 KeV = ideal peak for gamma camera imaging)	364 KeV	159 KeV	140 KeV
Availability and expense	Easily available, cheap	Less readily available expensive	Readily available, cheap
Radiation burden	High	Low	Lowest
Uses	Imaging and therapy	Imaging	Imaging
Uptake mechanism	Physiological: both trapped and organified	Physiological: both trapped and organified	Mimics iodide: Trapped but not organified
Imaging time after diagnostic dose administration	18–24 hours (post-therapy imaging at 1–5 days)	2–6 hours and 18–24 hours	20 minutes
Potential for stunning	Yes	No	No

following therapy. These drugs should be withdrawn a few days before treatment because of their theoretical radio-protective effects.<sup>7</sup> In patients with poorly functioning, non-toxic goitre, recombinant TSH is occasionally used to upregulate NIS and enhance <sup>131</sup>I uptake.

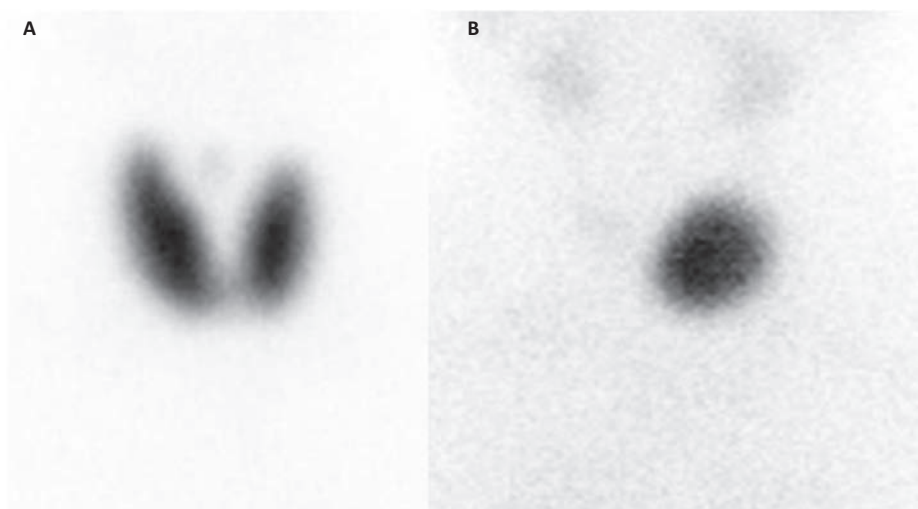
Although radioiodine treatment for benign thyroid disease is outpatient based, patients are requested to follow simple radiation protection restrictions post-treatment. These are related to the activity of radioiodine received and may include a period of time off work depending on the nature of work, travel restrictions and avoidance of prolonged close contact with children and pregnant women. Premenopausal women should also avoid pregnancy for 6 months following radioiodine treatment.<sup>11</sup>

Fixed activity regimens offer the advantage of ease of clinical prescription, outcomes with respect to euthyroidism and

hypothyroidism being dose dependent. Lower administered activities may reduce risks of hypothyroidism but carry an increased risk of treatment failure. Dosimetric approaches aiming to calculate a 'personalised' therapeutic dose of <sup>131</sup>I to achieve euthyroidism have not yet been shown to improve outcomes.<sup>12</sup>

### Malignant thyroid disease

Molecular radiotherapy plays a pivotal role in radio-sensitive differentiated papillary and follicular thyroid cancer (DTC) treatment.<sup>13</sup> Thyroid cancer may present clinically as a nodule or, increasingly, as an incidental imaging finding. While thyroid nodules are common, thyroid cancer is rare (UK incidence  $3.4 \times 10^{-3}$  cases/annum).<sup>14,15</sup>



**Fig 1. Scintigraphic imaging reflecting physiological and pathophysiological NIS-mediated iodide uptake in Graves' disease (A) and a toxic nodule (B).**

**Table 2. Guidance times for withholding substances that may interfere with NIS-mediated thyroid radio-pharmaceutical uptake prior to imaging**

Interfering substance	Recommended time to withhold prior to imaging
Anti-thyroid drugs	Pertechnetate imaging Can be continued $^{123}\text{I}$ or $^{131}\text{I}$ 2–4 days
Thyroxine ( $T_4$ ) therapy	4–6 weeks
Triiodothyronine ( $T_3$ ) therapy	2 weeks
Exogenous iodine (eg water-soluble iodinated contrast)	6–8 weeks
Amiodarone	Greater than 6 months

Adapted from Balon *et al.*<sup>8</sup>

DTCs are characterised by slow growth and favourable prognosis (80–95% 10-year survival). Local disease recurrence in the thyroid surgical bed, cervical nodes or distant metastases is reported in 5–20% of patients, depending on primary staging, histological subtype and nodal involvement at diagnosis.<sup>16</sup>

Surgery and  $^{131}\text{I}$  therapy are the cornerstones of DTC management. Following total thyroidectomy, usually with loco-regional node dissection,  $^{131}\text{I}$  is recommended to ablate normal thyroid remnant tissue, improve local disease control, increase the specificity of thyroglobulin (marker of tumour recurrence) and enable whole-body scintigraphy to identify occult metastases. TSH stimulation is used to upregulate NIS and maximise  $^{131}\text{I}$  uptake, either by post-thyroidectomy levothyroxine withdrawal or using recombinant human TSH.<sup>13</sup>

Fixed activities are prescribed to ablate the thyroid remnant while minimising the risk of inducing a secondary cancer. Following publication of the HiLo study, the recommended activity for remnant ablation in the UK is 1.1 GBq for low-risk patients. Higher activities may be agreed for high-risk patients (nodal or distant metastases, extra-thyroidal tumour extension, R1 resection (microscopic residual tumour at the surgical resection margin) or primary tumour size >4 cm) following multidisciplinary meeting discussion.<sup>17</sup> American

and European guidelines recommend activities of 1.1–5.5 GBq for the treatment of metastases.<sup>13,18</sup>

Post-ablation  $^{131}\text{I}$  imaging performed 1–5 days post-treatment is used to confirm remnant thyroid uptake and detect iodine-avid metastases. Tomographic imaging fused with CT (single photon emission computerised tomography (SPECT)–CT), increases lesion detection sensitivity and provides accurate anatomical localisation. Having commenced post-ablation levothyroxine replacement to achieve TSH suppression, subsequent monitoring usually relies on ultrasound and thyroglobulin measurement. Further cycles of therapeutic  $^{131}\text{I}$  may be required to treat persisting iodine-avid metastases.

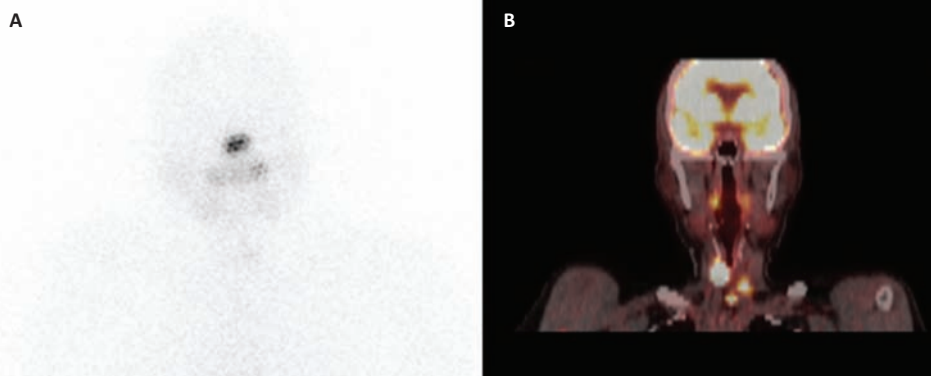
Diagnostic  $^{123}\text{I}$  scintigraphy is sometimes helpful to detect occult disease, post thyroid remnant ablation, where other imaging has failed to identify the source of a rising thyroglobulin level.  $^{123}\text{I}$  avoids the risk of ‘stunning’ and is preferred to  $^{131}\text{I}$  in patients who might proceed to further radioiodine treatment. Increasingly, however,  $^{123}\text{I}$  has been superseded by  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) positron emission tomography (PET)–CT in patients with increasing thyroglobulin and non-iodine avid disease to exclude surgically resectable disease, followed by empirical  $^{131}\text{I}$  treatment.

Two-thirds of patients with metastatic disease become refractory to radioiodine because of tumour de-differentiation resulting in decreased NIS expression and/or targeting secondary to genetic alterations and dysregulation of signalling pathways.<sup>19</sup> De-differentiated, recurrent iodine-negative lesions tend to have high glycolytic rates and are therefore FDG-avid. This inverse relationship between iodine and FDG-avidity (Fig 2), depending on differentiation, probably reflects tumour heterogeneity and importantly may result in a poor response to  $^{131}\text{I}$  treatment. Positive NIS-immunostaining could predict  $^{131}\text{I}$  accumulation and, therefore, the effectiveness of treatment in recurrent lesions.<sup>20</sup>

Advances in molecular biology have identified specific molecular kinase pathways where oncogenic mutations have resulted in reduced NIS expression/targeting.<sup>21</sup> Tyrosine kinase inhibitors (eg sorafenib) block these pathways, increasing NIS expression. The mitogen-activated protein kinase pathway inhibitor sunitinib has also been shown to promote  $^{131}\text{I}$  uptake in a small series of patients with iodine-refractory thyroid cancer, but this requires confirmation in larger studies.<sup>22</sup>

Re-differentiation therapies (eg retinoic acid) upgrade NIS and may restore  $^{131}\text{I}$  avidity. In some non-iodine avid thyroid

**Fig 2. Inverse relationship between iodine and FDG avidity – a reflection of tumour differentiation.** A –  $^{131}\text{I}$ -radioiodine anterior neck image shows no iodine avid disease within the neck (salivary gland and nasal uptake is physiological); B –  $^{18}\text{F}$ -FDG PET-CT coronal fused image shows bilateral FDG-avid neck disease. CT = computerised tomography; FDG = fluorodeoxyglucose; PET = positron emission tomography





cancers the problem lies in NIS cell membrane translocation. Enhancing this may aid therapeutic  $^{131}\text{I}$  uptake.<sup>19</sup> An alternative approach lies in detailed dosimetry planning to deliver a prescribed tumour radiation dose. Considering anatomical and uptake characteristics of each malignant lesion, dosimetry-based planning offers the opportunity to optimise treatment on an individual patient-basis, rather than administering fixed  $^{131}\text{I}$  activities. SPECT-CT technology is critical to undertaking 3-dimensional absorbed-dose calculations.

### Future directions

$^{124}\text{I}$  is currently the only positron-emitting radioisotope of iodine that may have a role in molecular thyroid radiotheragnostics in the future.  $^{124}\text{I}$ -PET-CT has the potential advantage of superior image quality and might allow more accurate quantification to optimise prescribed amounts of therapeutic  $^{131}\text{I}$ .

Tumour heterogeneity, oxygenation and cell kinetics all affect dose-response relationships. Tumour apoptosis, hypoxia and cellular proliferation may be assessed by radioactive tracers, such as  $^{99\text{m}}\text{Tc}$ -annexin V,  $^{18}\text{F}$ -fluoromisonidazole and  $^{18}\text{F}$ -fluorothymidine, and used to predict therapeutic response to  $^{131}\text{I}$ .

### Conclusions

The established role of nuclear medicine imaging and therapy in managing benign and malignant thyroid disease is the oldest and, arguably, most successful example of molecular radiotheragnostics. The future lies in advances in molecular biology, the development of agents that increase NIS expression, dosimetry-based treatment planning and the introduction of novel PET radiopharmaceuticals, all of which have the potential to deliver the goal of a personalised medicine approach to thyroid disease. ■

### Conflicts of interest

The authors have no conflicts of interest to declare.

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